DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

CSO Label Review

NDA: 20-412/SLR-015
20-413/SLR-006

Date submitted: January 4, 2001
Date received: January 5, 2001

Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute
5 Research Parkway
Wallingford, CT 06492

Products: ZERIT® (stavidine) Capsules
ZERIT® (stavidine) POS

Materials Reviewed: Final Printed Labeling dated January 4, 2001 and February 6, 2001.

Background:

On January 4, 2001, Bristol-Myers Squibb submitted these supplements to support a change in the Black Box Warning, WARNINGS, and Precautions sections of the ZERIT® label. These changes were implemented as a Special Supplement, Changes Being Effected (CBE) after negotiations with DAVDP regarding the wording, and reflect new information regarding fatal lactic acidosis in pregnant women. The implementation of this label was accompanied by a "Dear Health Care Provider" letter, which warned clinicians of this potential risk. DAVDP agreed on proposed wording on January 2, 2001, and the Final Printed Labeling was sent electronically on January 4, 2001.

Label Revisions:

1. Addition of a new Black Box Warning, as follows:

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING STAVUDINE AND OTHER ANTIRETROVIRALS. FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF STAVUDINE AND DIDANOSINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF STAVUDINE AND DIDANOSINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS: PREGNANCY).

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN ZERIT WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE, WITH OR WITHOUT HYDROXYUREA, IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS).

2. Deletion of the following words in the **CLINICAL PHARMACOLOGY**, Special Populations, Race section:

   The results of this analysis…

3. The addition of the following wording in the **WARNINGS**, Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic failure section:

   Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see **PRECAUTIONS: Pregnancy**)

4. The addition of the following words to the **PRECAUTIONS: Pregnancy** section, last sentence of the first paragraph:

   Animal…response.

5. The addition of the following sentence to the **PRECAUTIONS: Pregnancy** section, last sentence of the first paragraph:

   There are no adequate and well-controlled studies of stavudine in pregnant women.

6. The addition of the following words to the **PRECAUTIONS: Pregnancy** section, last sentence of the third paragraph:

   …women receiving…alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

7. All such terms "BID" have been replaced with the following:

   twice-daily

Conclusions/Recommendations:

It should be conveyed to the applicant that the Final Printed Labeling is acceptable, and an approval letter should be sent.

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Regulatory Project Manager